Polymers from Sugars and CO_2: Synthesis and Polymerization of a D-Mannose-Based Cyclic Carbonate

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ABSTRACT: A six-membered cyclic carbonate derived from natural sugar D-mannose was prepared using CO_2 as a C1 building block at room temperature and atmospheric pressure. The monomer was synthesized in two steps from a commercially available mannopyranose derivative. Polycarbonates were rapidly prepared at ambient temperature by controlled ring-opening polymerization (ROP) of the monomer, initiated by 4-methylbenzyl alcohol in the presence of 1,5,7-triazabicyclo[5.4.0]dec-5-ene (TBD) as the organocatalyst. Head-to-tail regiochemistry was indicated by NMR spectroscopy and is supported by DFT calculations. These aliphatic polycarbonates exhibit high-temperature resistance and demonstrate potential for post-polymerization functionalization, suggesting future application as high-performance commodity and biomedical materials.

Introduction

The development of sustainable polymers from renewable feedstocks is important to address the dependence of most engineering and commodity plastics on fossil-based resources.[1] Natural sugars are one such raw material attracting increased research attention as petroleum-based alternatives in polymer synthesis due to their high abundance, low toxicity and structural diversity.[2] In particular, carbohydrates having a cyclic structure can impart stiffness into the polymer chain, increasing the glass transition temperature.[3] Herein, we report the synthesis and controlled polymerization of a novel cyclic carbonate monomer prepared from D-mannose and CO_2, which yields polycarbonates with enhanced thermal properties compared to traditional aliphatic polycarbonates.

The combination of biodegradability and biocompatibility has led to the emergence of aliphatic polycarbonates (APCs) as attractive materials for biomedical applications such as tissue engineering scaffolds and vehicles for drug-delivery.[4] However, the hydrophobicity, poor cell compatibility, and low glass transition temperatures (T_g) of unfunctionalized APCs such as poly(trimethylenecarbonate) ($T_g \approx -20$ °C) has instigated a drive towards the development of functionalized APCs with tailored properties.[5] Due to their wide structural diversity and natural origin, sugar-based polycarbonates offer the potential for highly biocompatible, degradable materials as well as drawing upon renewable feedstocks.

Ring-opening polymerization (ROP) of 6-, 7-, 8-[6] (and highly strained 5-[7]) membered cyclic carbonates is an attractive method for polycarbonate production.[8] Compared to the polycondensation of aliphatic diols with phosgene derivatives or dialkyl carbonates, which often presents challenges in molecular weight control,[9] developments in ROP catalysis have enabled polymerizations to proceed in a controlled fashion under mild conditions.[10] Furthermore,

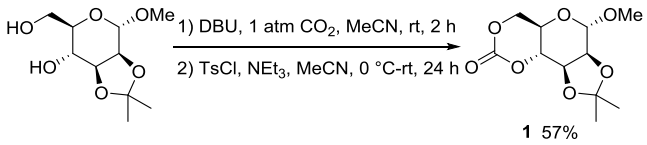
advances in organocatalytic ROP have provided alternatives to traditional heavy metal based catalysis.[11] By way of a sustainable approach, utilization of CO_2 as an abundant, safe and renewable building block has also led to the continued development of catalysts for the synthesis of APCs by the alternating ring-opening copolymerization (ROCOP) of CO_2 with epoxides.[12] However, the epoxide scope can be limiting compared to the versatility of catalytic ROP methods and the wide range of functionalities offered by cyclic carbonates, which are commonly obtained by cyclocarbonation of readily available and diverse diols. Nevertheless, there are few examples reported for the ROP of cyclic carbonates bearing a carbohydrate backbone[13] due to challenges in the cyclization of sugar-derived diols or in the polymerization itself.

Gross and co-workers reported for example the synthesis, of a D-xylose-derived 6-membered cyclic carbonate using ethyl chloroformate.[13b] However, subsequent ROP of the *cis*-configured monomer containing a ketal-protected vicinal diol proved challenging. Rare-earth catalyst $Y(O\textit{i}Pr)_3$ displayed the best activity for achieving high molecular weights, reaching 13.2 kDa after 3 h at 70 °C in dioxane with a dispersity index (Đ) of 1.69. More recently, Wooley and co-workers showed that bis(pentafluorophenyl) carbonate and CsF were required to cyclize the *trans*-configured 4,6-diol in trimethyl-protected D-glucose, giving a 36% isolated yield of a bicyclic monomer after 25 h at 60 °C.[13d] Polymerization initiated by 4-methylbenzyl alcohol then proceeded readily at room temperature with organocatalyst 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), to give good control over polymer molecular weights and narrow molecular-weight distributions. Thermal analysis proved promising for both polymers, revealing high T_g values of 106 and 128 °C, respectively.

Building upon our previous report for the preparation of cyclic carbonates from diols and low pressure CO_2 as an alternative to phosgene-based methods,[14] we investigated the synthesis of D-

mannose derived cyclic monomer **1** (Scheme 1). Thus, both CO_2 and sugars would be used as safe, natural and renewable resources in material synthesis. Furthermore, the D-mannose natural stereochemistry would combine the attractive components of both glucose- and xylose- based monomers previously reported, namely an easily ring-opened *trans*-cyclic carbonate and a protected 1,2-diol motif, to serve as a handle for post-polymerization modification.

Scheme 1. Cyclization of protected D-mannose using 1 atm CO_2 at room temperature (rt).



1 57%

Results and Discussion

The monomer was readily prepared in two steps from commercially available 1-*O*-methyl-α-D-mannose. Following isopropylidene protection of the hydroxyl groups at the 2 and 3 positions, cyclic carbonation was achieved using CO_2 as a C1 synthon. CO_2-insertion with 1 equiv. of 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) reagent to form an ionic salt intermediate, a method of CO_2 capture with alcohols initially reported by Jessop *et al.*,[15] resulted predominantly in mono-insertion into the less sterically hindered primary hydroxyl group, as indicated by $^{13}C\{^1H\}$ NMR spectroscopy (Figure S1 in the Supporting Information (SI)). Addition of the tosyl chloride leaving group led to formation of the monomer in 65% conversion *via* a nucleophilic addition-elimination pathway. High dilution conditions (0.1 mol L^{-1}) and cold temperatures were key in favouring the desired unimolecular cyclization over competing dimerization reactions. Isolation by column chromatography and subsequent recrystallization in diethyl ether afforded the desired compound, cyclic 1-*O*-methyl-2,3-*O*-isopropylidene-4,6-*O*-carbonate-α-D-mannopyranose **1** in 57% yield (compared to 36% and 41% isolated yields for the previous glucose- and xylose-based

monomers that were synthesized using phosgene derivatives). Attempts to synthesise **1** using 1,1'-carbonyldiimidazole or CO_2 over CeO_2 as reported by Honda *et al.*[16] proved unsuccessful giving 0% conversion. Confirmation of the structure by NMR and FTIR spectroscopies, as well as electrospray ionisation mass spectrometry, were further corroborated by single-crystal X-ray diffraction (Figure 1 and Figures S2-S8). The $^4C_1$ chair conformation of the pyranose ring placing bonds C11-O3 and C3-C2 di-equatorial allows for the strained *trans*-configured cyclic carbonate.

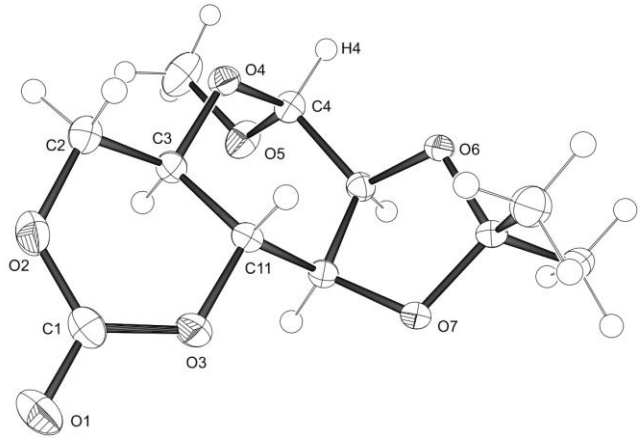


Figure 1. ORTEP[17] view of the crystal structure of **1** with key atoms labelled. Displacement ellipsoids at the 50% probability level.[18] Selected bond lengths (Å) and angles (°): C(1)-O(1) 1.198(2), C(1)-O(2) 1.333(2), C(1)-O(3) 1.341(2), O(1)-C(1)-O(2) 120.38(14), O(1)-C(1)-O(3) 119.57(15), O(2)-C(1)-O(3)120.05(14), C(2)-C(3)-C(11)-O(3) 56.10(15).

Organocatalytic ROP of **1** with TBD catalyst and 4-methylbenzyl alcohol initiator proceeded rapidly at room temperature, reaching >99% conversion in 1.3 h at a monomer to initiator feed ratio of 100, and 1 mol% catalyst. Monomer conversion was determined by ^{1}H NMR spectroscopy (Figure 2) and number average molecular weights (M_n) alongside dispersities (Đ) estimated by Size-Exclusion-Chromatography (SEC) relative to polystyrene standards. The linear relationship between monomer conversion and M_n at constant monomer to initiator ratio,

coupled with consistently narrow dispersities (1.12-1.17) was indicative of a well-controlled polymerization (Figure 3). MALDI-ToF analysis revealed a linear polymer series with no evidence of decarboxylation, and confirmed the expected 4-MePhCH$_2$O and OH end groups (Figure S22).

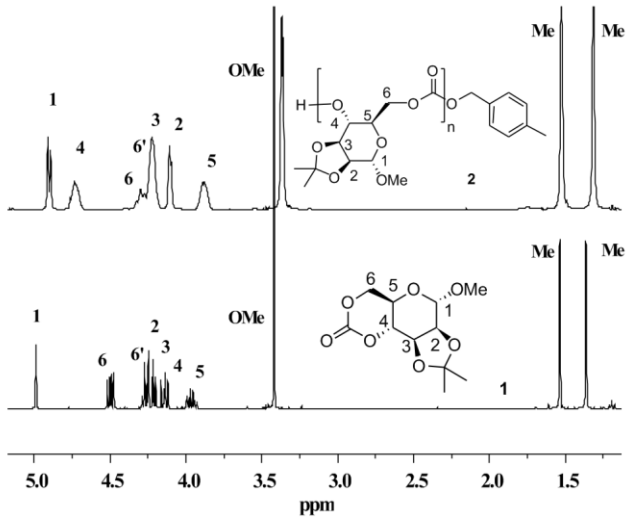


Figure 2. ^{1}H NMR spectra of monomer **1** (bottom) and polymer **2** (top) in $CDCl_3$.

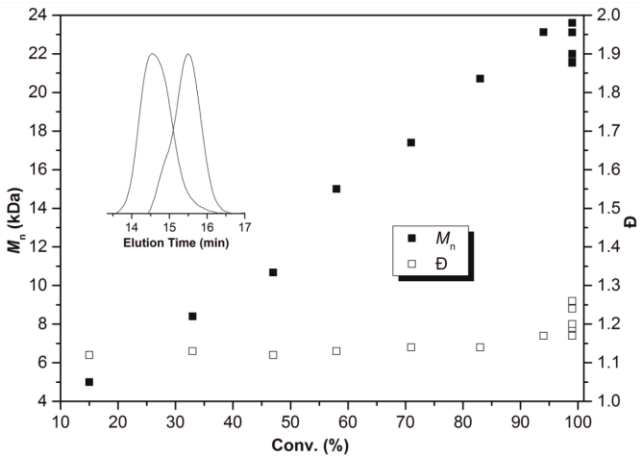
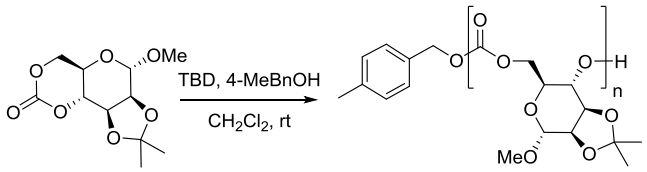


Figure 3. Plot of M_n (■, left axis) and Đ (□, right axis) estimated by SEC (RI detector) relative to polystyrene standard *vs.* conversion of monomer **1** (determined by integration of the anomeric proton in the ^{1}H NMR spectrum). Aliquots were taken and quenched every 10 minutes from a reaction in CH_2Cl_2 at rt, with a $[\mathbf{1}]_0$:$[TBD]_0$:$[4\text{-MeBnOH}]_0$ ratio of 100:1:1 and $[\mathbf{1}]_0$ = 1 mol L^{-1};

(inset) Typical SEC trace showing increase in M_n from 5.36 to 10.5 kDa (maintaining Đ = 1.15) upon addition of 0.5 equiv. of **1** to a polymerization [**1**]/[4-MeBnOH] = 25 at >99% conversion.

Linear plots of $\ln([\mathbf{1}]_0/[\mathbf{1}])$ against time at 100:1:1 and 50:1:1 $[\mathbf{1}]_0$:$[TBD]_0$:$[4\text{-MeBnOH}]_0$ ratios indicated first order kinetics in monomer concentration (k_{app} = 1.7 ± 0.1 h^{-1} and 9.9 ± 0.8 h^{-1} respectively, Figure S28), typical of ROP. Further polymerization experiments were performed over a range of catalyst concentrations (Table 1), showing close agreement between the calculated molecular weights and those determined by SEC relative to polystyrene standards. Polymers exhibited low molecular-weight distributions and incorporation of additional monomer after full conversion was reached further confirmed the well-controlled living nature of the polymerizations (inset SEC trace, Figure 2). Moreover, a polymer with M_n 7.36 kDa estimated by SEC showed good correlation with M_n values derived from ^{1}H NMR spectroscopy (6.95 kDa) and MALDI-ToF analysis (7.55 kDa). Prolonged reaction times of 2 and 4 h led to a decrease in M_n and broadening of the dispersity to 1.3. In addition, although SEC traces were unimodal at lower molecular weights, above ~15 kDa a shoulder or slight bimodality was observed. Collectively, we suggest this is a result of the backbiting of the polymer chain to form smaller cyclic species. This is supported by MALDI-ToF mass spectrometry which revealed a series with sugar carbonate repeat units and no end-group (Figure S25). Monomer-to-initiator ratios greater than 150 (Table 1, entry 7) resulted in significant backbiting, even at high dilution, as well as leading to the formation of a THF-insoluble polymer, which eluded SEC analysis. Polymerization could also be carried out under industrially relevant conditions, in the melt at 140 °C with TBD and $Sn(Oct)_2$ catalysts (Table 1, entries 8 and 9).

Table 1. Organocatalytic ROP of 1 by TBD with 4-methylbenzyl alcohol initiator.[a]



1 **2**

entry	$[\mathbf{1}]_0$:$[C]_0$:$[I]_0$[b]	conv. (%)[c]	time (h)	M_n [Đ] (kDa)[d]	calc. M_n (kDa)[e]
1	25:1:1	>99	0.5	6.63 [1.15]	6.56
2	50:1:2	>99	0.5	6.26 [1.15]	6.56
3	50:1:1	>99	1	13.6 [1.17]	13.0
4	100:1:2	>99	1.5	10.8 [1.10]	13.0
5	100:1:1	47	0.5	10.7 [1.12]	12.3
6	100:1:1	>99	1.3	23.6 [1.17]	25.9
7	150:1:1	98	3	33.4 [1.19]	38.3
8[f]	100:1:1	98	0.5	26.2 [2.15]	25.6
9[g]	100:0.5:1	60	0.5	10.9 [1.22]	15.7

a) Polymerizations carried out in CH_2Cl_2 at room temperature, with $[\mathbf{1}]_0$ = 1 mol L^{-1}, unless stated otherwise b) C is TBD, I is 4-MeBnOH unless stated otherwise. c) Determined by relative integration of the anomeric proton in the ^1H NMR spectrum in $CDCl_3$. d) Calculated by SEC relative to polystyrene standard with THF eluent; Đ = M_w/M_n. e) Calculated as $M_r(I) + (M_r(\mathbf{1}) \times [\mathbf{1}]_0/[I]_0 \times$ conv./100%). f) Melt conditions: 140 °C. g) C: $Sn(Oct)_2$, melt conditions: 140 °C.

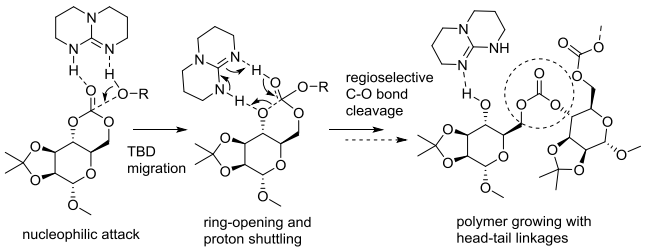
The polycarbonate is characterised by a strong C=O absorption at 1757 cm^{-1} in the FTIR spectra. Conformational changes brought about by the release of ring strain upon opening are

most evident in the ^{1}H NMR spectrum (Figure 2) by the downfield shift of H-4 and coalescing of the signals assigned to H-6 and H-6'. In the $^{13}C\{^{1}H\}$ NMR spectrum, one distinct carbonyl resonance is observed at 154.5 ppm (Figure S16) compared to the monomer signal at 147.4 ppm. This contrasts with the D-xylose- and D-glucose-based polycarbonates, for which three distinct carbonate environments (differing by 0.3-0.5 ppm), were observed and assigned to tail-tail (T-T), head-tail (H-T) and head-head (H-H) carbonate linkages (Figure S29). Their 1:2:1 ratio suggested random cleavage of the acyl-oxygen bond at either side of the carbonate carbonyl and subsequent non-selective propagation of the chain to yield regiorandom polymers.[13d] Thus the carbonate region of **2** suggests a preference for one regiochemistry, specifically H-T linkages as any H-H (or T-T) linkages would also entail T-T (or H-H) linkages and yield two distinct resonances. The equimolar experiment between **1** and 4-MeBnOH in the presence of 2 mol% TBD revealed (by NMR spectroscopy) an 88% preference for ring-opening to place the benzyl carbonate at the less sterically hindered primary position, leaving the secondary hydroxyl group free (Figure S30 and S31). A similar regioselective ring-opening was recently reported by Sopeña *et al.* in the synthesis of carbamates using TBD.[18]

The reaction mechanism between TBD, 4-methylbenzyl alcohol and up to two molecules of **1** (to account for both initiation and propagation steps) was also examined using DFT calculations.[19] In accordance with previous calculations,[6] TBD acts as a bifunctional catalyst, capable of activating the carbonate monomer but also of deprotonating the growing alcohol chain. The ring-opening is then a discrete, rather than concerted, process, with TBD mediating proton transfer stepwise through tetrahedral intermediates. In agreement with the experimental findings, the initiation step was found to favor, both kinetically and thermodynamically, ring-opening to expose a secondary alcohol (Figures S40-41). Regardless of the regioselectivity of the

initiation step, subsequent propagation from either a primary or secondary growing polymer chain shows the same bias, leading to an overall preference for head-tail linkages (Scheme 2 and Figure S42-45). The lowest limiting energy barriers found, $\Delta\Delta G$ of +9.2 and +13.7 kcalmol^{-1} for the initiation and propagation steps respectively, are low enough for the reaction to proceed readily at room temperature. The overall ΔG is calculated to be –11.4 kcalmol^{-1} for initiation, and –1.8 kcalmol^{-1} for the propagation step. Finally, calculations indicate that the ring-opening thermodynamics of **1** are very similar to those of the D-glucose monomer reported by Wooley and coworkers[13d] (Schemes S1 and S2), suggesting that the regioregularity of polymer **2** compared to its glucose counterpart is of kinetic origin. This is likely a result of the additional steric constraint imposed by the 2,3-*O*-isopropylidene protecting group.

Scheme 2. Mechanism of regioselective ROP of **1** leading to regioregular **2**, as supported by DFT calculations (ROH= primary or secondary alcohol chain).



The mannose polycarbonates are amorphous in character, showing no sign of crystallinity by powder X-ray diffraction (Figure S32). Evaluation of the thermal properties by thermogravimetric analysis (TGA) of representative samples coupled to a mass spectrometer showed the onset of thermal degradation at ≈ 170 °C, reaching a maximum degradation rate around 259 °C and resulted in 98% mass loss by 350 °C (Figure S34). Major ions detected at *m/z* 44 and 58 were attributed to the loss of CO_2^+ and $(CH_3)_2CO^+$, respectively (Figure S35). Differential Scanning Calorimetry (DSC) (Figures S36 and S37) revealed high glass-transition

temperatures (T_g = 152 °C for 13.6 kDa, Table 1, entry 3), compared to reported glucose (T_g = 122 °C for 14.7 kDa)[13d] and xylose (T_g = 128 °C for 13.2 kDa)[13d] polycarbonates. The elevated T_g arise from restricted rotation about the polymer backbone which are likely due to the rigid bicyclic nature of the protected mannose unit, and make these materials attractive for the construction of new high-performance sustainable materials.[20] Indeed, a high T_g is an important consideration in materials for tissue engineering scaffolds as it corresponds to a low free volume in the polymer network which limits the access of water, resulting in enhanced stability to hydrolytic degradation.[21] Deprotection of the pendant ketal groups to expose the vicinal diol was explored by treatment of **2** in $CDCl_3$ with 80:20 CF_3COOH:H_2O.[22] Removal of 70% of the protecting group (determined by relative integration of the OMe and *i*Pr proton environments) was achieved whilst maintaining solubility in $CDCl_3$, and showed no visible signs of degradation (Figure S39). SEC analysis confirmed the material to still be polymeric. Further deprotection rendered it insoluble in $CDCl_3$ and THF, with no free monomer observed in solution. The initial fully-protected polymer was insoluble in water and found to resist acid hydrolysis (HCl_{aq} 1 mol L^{-1}) over 14 days. Detailed studies into the mechanical properties, degradation behavior and biocompatibility of these polymers are in progress, including post-polymerization functionalization and cell-attachment work.

Conclusion

In conclusion, we have demonstrated the novel synthesis, using CO_2, and the controlled organocatalytic ROP, of a new cyclic carbonate monomer derived from D-mannose. NMR analyses supported by DFT calculations suggest the formation of regioregular polycarbonates

composed of head-tail linkages. High glass transition temperatures compared to other APCs highlight the potential of these materials in future commodity and biomedical applications.

ASSOCIATED CONTENT

Supporting Information. Experimental and computational details; spectroscopic and crystallographic characterization data for **1**; SEC traces, MALDI-ToF spectra, spectroscopic and thermal (TGA, DSC) data for **2**; DFT calculations data and associated digital repositories. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interests.

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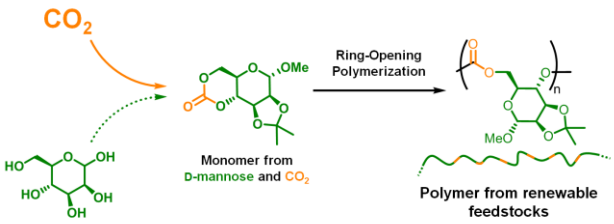

Polymers from Sugars and CO_2: Synthesis and Polymerization of a D-Mannose-Based Cyclic Carbonate

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